NOMA: GANGRENOUS STOMATITIS, WATER CANCER, SCORBUTIC CANCER, GANGRENA ORIS, GANGRENE OF THE MOUTH

GEORGE H. WEAVER AND RUTH TUNNICLIFF

Reprinted from
THE JOURNAL OF INFECTIOUS DISEASES, Vol. 4, No. 1, January 1, 1907, pp. 8–35

CHICAGO

NOMA.*†

(GANGRENOUS STOMATITIS; WATER CANCER; SCORBUTIC CANCER; GANGRENA ORIS; GANGRENE OF THE MOUTH.)

GEORGE H. WEAVER AND RUTH TUNNICLIFF.
(From the Memorial Institute for Infectious Diseases, Chicago.)

INTRODUCTION.

TOURDES has defined noma as a gangrenous affection of the mouth especially attacking children in whom the constitution is altered by bad hygiene and serious illness, especially from the eruptive fevers, beginning in an ulcer of the mucous membrane with edema of the face, extending from within out, rapidly destroying the soft parts and the bone, accompanied most often by hepatization of the lungs, and almost always quickly fatal. Other writers have included under this head all of the gangrenous processes which involve the skin of children. There has been much difference of opinion as to the relationship borne by various ulcerative processes in the mouth to noma. Some of the studies carried on during the past few years seem to point to a common etiology for many of the pseudo-membranous and ulcerative lesions of the naso-pharyngeal mucous membrane and for noma, the difference in the degree of destruction of tissue depending upon varying degrees of vulnerability of the tissues, and perhaps in a less degree upon varying degrees of virulence of the bacteria concerned.

In the following article we shall use the word "noma" as a term to cover all these forms of gangrene which involve the mucous membrane and skin with the intervening isssues in the neighborhood of the orifices of the body.

HISTORICAL SKETCH.

Such a striking and fearful disease as noma could not fail to be noted by the first physicians who came in contact with it. That this was the case is evident from the abundant literature relating to it collected by A. L. Richter in his publications in 1828, 1832, and 1834. Richter was the first author of a monograph upon noma, and in his first publication he collected 74 references to this disease in the literature. They were gleaned from the various parts of the world. A few of the earlier historical facts connected with the disease are given here, many being quoted from Richter's monograph.

The disease was known to the most ancient medical writers, such as Hippocrates, Galen, Celsus, Arethaeus, Caelius Aurelianus, and Alexander de Tralles. Hippocrates applied the name noma to all kinds of gangrene and ulcers, and connected it especially with putrid decomposition and considerable destruction of tissue. Galen mentions noma in many passages of his work. He defines it as an affection characterized by destruction of tissue extending from the diseased parts to the healthy. He also connected noma and putrid decomposition. He classed together noma and

* Received for publication, May 1, 1906.

† In the study of the case of noma herein reported, a review of literature covering many years was undertaken. With the hope of sparing some of this labor to those who in the future may have occasion to study such cases, an effort has been made to incorporate in this article the most important facts bearing upon the subject.

the affections of the mouth, anus, and genitalia. He recommended for treatment aromatics, stimulants, and caustics, and recognized the necessity of the red-hot iron. Celsus, who is credited with giving the most precise description, according to Tourdes, was not describing noma but malignant pustule. Arethaeus described an aphthous ulceration which had many analogies to the gangrenous affections of the mouth. Caelius Aurelianus and Alexander Trallianus both used the term noma with the idea of putrid decomposition. Noma was probably rarer then than later, because the conditions predisposing to it were less prevalent. The absence of hospitals and the eruptive fevers account for its infrequent occurrence in ancient times, according to Tourdes.

Baltus, in 1620, a Dutch surgeon, furnished the first accurate description of gangrene of the mouth in his *Handbook of Surgery*. Van de Voorde (1662), introduced the name "water-kanker," which was usually employed by subsequent Dutch writers. Van Swieten gave it the name "gangrene." J. Van Lil called it "ulcus noma, stomacace, and water-kanker." He referred to many Dutch authors who observed epidemics of the disease following exanthematous diseases. Most of the Dutch writers pointed out the influence of scurvy on this condition.

Swedish physicians were also familiar with the nature and course of the disease. Lund based his writings on 11 cases, only one of which recovered. He recognized the fact that it occurred only among the children of the poor who lived in damp, unhealthy atmosphere and were poorly nourished. Leutin described the disease most accurately under the name of "ulocace."

In England, Boot first described the disease. Subsequent writers in England were Underwood, Symmonds, Pearson, S. Cooper, Marshall-Hall, West, and others.

In America the disease was early described by Coates, Gerhard, Meigs and Pepper. Coates, writing in 1826, states that ever since the establishment of the Children's Asylum in Philadelphia, in the spring of 1819, the institution had been annually visited by the new and distressing scourge. He further says: "It has here prevailed in a considerable number of cases, forming the principal source of anxiety and trouble during the winter season, and annually sweeping off its little victims in a manner rendered peculiarly awful by its insidious approach, its loathsome effects, and its apparently uncontrollable progress." He observed 70 cases among 240 children, but from his description he evidently included cases of ulcerative stomatitis. Coates says the disease was rare in Philadelphia, but quite prevalent in Salem, N. J. He refers to other American authors who had observed cases of the disease.

German physicians have furnished the most and best monographs upon this disease. Preceding A. L. Richter it was carefully studied by Fabricius von Hilden under "de catarrho ad gingivas," by A. G. Richter, and by Jawandte under "noma or gangrene of the mouth." Wendt recognized it as the most fearful sequel of scarlatina and measles, and called it "sphacelus" of the mouth. C. F. Fischer and Siebert sought especially to turn attention to this disease. The latter believed a scorbutic disposition essential for its development, and emphasized the value of local remedies, especially acids. Hildebrand, Girtanner, Fleisch, Feiler, Henke, Jörg, and Raimann held that water cancer is the latest stage of the symptoms belonging to scorbutus. Raimann discarded the name cancer, and proposed that of very acute, pultaceous or caseous gangrene. Wiegand and Klaatsch undertook to differentiate between water cancer and scorbutus. In 1828 A. L. Richter published the first monograph on noma, under the title of *Wasserkrebs*, and in 1832 he completed it by a supplement. His

collection of the literature up to that time is so complete that subsequent writers have found it needless to go back of his work.

In France the disease had early received much attention. Poupart and Saviart observed gangrene of the mouth in Hôtel-Dieu. Berthe described it under the name, "scorbutic gangrene of the gums" ("gangrène scorbutique des gencives"). Sauvages described it under "necrosis infantilis." Baron in 1816 published a description of the disease, and concluded that gangrene of the mouth is an affection *sui generis*, and local. He found the best treatment, if perforation has occurred, to be the hot iron. In 1818, Isnard, in his inaugural thesis, described gangrene of the mouth and vulva. He favored the use of the actual cautery after excision of gangrenous tissue. Some less important publications by Cliet, Rey, Destrées, Billard, Murdock, Boeckel, Constant, Taupin (1839), and others, were followed by the very complete monograph by Tourdes in 1848. Bouley and Caillault published a valuable contribution in 1852. This brings us up to the publication of the most comprehensive description by Barthez and Rilliet in 1855. Among the more recent noteworthy and exhaustive writings upon noma may be mentioned those of Bruns in 1859, Gierke in 1868, Hirsch 1862–64, and Bohn in 1880.

Bruns says that Uzanam in 1823 describes the disease occurring in Spain, as "fegra," "fegar, "or "fegarite." In 1810 it occurred among the French troops in Madrid, attacking more than 100. It was said to occur among children in Spain, appearing to be contagious. Gangrene of the mouth appears to have been rare in Italy. Benevoli, Bartholomeo, Maggi, and Joanès Togault are mentioned by German writers as contributing articles on the subject of noma.

FREQUENCY OF OCCURRENCE.

Noma is an uncommon disease. In private practice it is almost never met with, and the experience of Meigs, who "never met with a case in private practice," corresponds with that of most practitioners. Even in hospitals the disease is uncommon. Allbutt says that only one case appeared on the records of Westminster Hospital in 10 years. According to Allchin, at the East London Hospital for Children, which is situated in a very poor and densely crowded district, during seven years, 1881–87 inclusive, only five cases occurred in a total of 6,364 admissions during that time. At Great Ormond Street Hospital, during 13 years, 1876–88, only six cases occurred, with a total of more than 13,000 patients.

In some continental hospitals the proportion of cases seems larger. Gierke states that during 16 years, 20 cases were observed in the Children's Hospital of Stettin. In the Children's Hospital in Prag, according to Springer, 65 cases occurred in 30 years from 1857 to 1887, and 23 cases in the 16 years from 1888 to 1903. Woronichin saw noma occur in 22 out of 8,286 hospital patients, and in 24 out 207,259 ambulatory patients.

ETIOLOGY.

Age.—Noma is a disease which occurs almost exclusively in young children. The largest number of the cases are observed between the second and seventh years of age, a few being seen in the first year, and occasional ones up to the twelfth. According to Tourdes many physicians believed that immunity was acquired against the disease during the period of lactation. This author (1848) reported nine authors who had seen noma in persons between 15 and 72 years of age. Bruns in 1859 referred

to 11 authors who had observed cases in persons between the ages of 15 and 70. In 1872 Struch reported a case in a man 30 years old. It was unusual in that it could not be traced to any other disease, the patient apparently being in good health when the gangrenous process began. He referred to a case observed by Vogel in a patient 18 years of age also with no apparent cause. Masterman in 1891 recorded two cases in adults in which no cause could be found. In 1873 Hildebrand (quoted by Ziegler) collected 22 cases from the literature in persons over 15 years of age. In most cases it followed acute infectious diseases, especially measles. Other more recent authors have reported cases in adults following infectious diseases: Brydon, after erysipelas of the leg, at 47 years; Zieger, at 28 years; Köster, following hemorrhagic pleuritis; LeCount, following amebic dysentery; Kraus, after typhoid fever. Herff, under hospital gangrene of the vulva, and Herman, under acute gangrene of the vulva, have reported cases which perhaps belong in the same group.

Sex.—It has been said by Tourdes and others that noma is more frequent in girls than boys. This is explained by the inclusion in the statistics of cases of noma of the genitalia, this location of the disease being observed quite frequently in girls. Girls do not appear to be more susceptible, but present greater opportunities for local predisposing conditions.

Hygienic conditions.—Most authors have laid much stress upon a constitutional condition which must be present in order for the disease to occur. Richter believed the cause must be sought in the organism of the child. Barthez and Rilliet say that it usually occurs in weakly children. Gierke's cases all occurred in poorly nourished anemic children from poor families. Mayr, writing of noma cases accompanying or following measles, insisted that depressing conditions other than measles are always necessary. According to Barthez and Rilliet, it sometimes occurs in strong children. Strueh referred to four cases reported by Rust, Siebert, and Klaatsch, in well nourished children, without preceding sickness. Cases in apparently healthy adults have already been referred to.

Noma has generally been said to be a disease of the children of the poor, and is apt to occur in conditions of uncleanliness, over-crowding, damp, bad air, and poor food. Boeckel (cited by Tourdes) reported a case in a child living under the best hygienic conditions. Gierke noted that it might occur in good surroundings in poorly nourished children in the course of certain diseases. Coates's cases occurred in a hospital hygienically located, and the epidemic reported by Blumer and MacFarlane occurred in a modern hospital in which the general hygienic and dietetic conditions were excellent. The occurrence appears to be dependent more upon the individual than upon surroundings, except as the latter, if bad, may lower the resistance of the individual, and favor the development of weakly children.

Climate.—That climate may play a part has been pointed out by Tourdes and Barthez and Rilliet, who say that the disease is endemic in cold and damp climates, as Holland, Sweden, and the Prussian coast. However some of the larger groups of cases have been observed in inland cities. Tourdes mentions its presence in marshy countries.

Season.—It is usually stated that the cases occur most often in the winter, rarely in the summer. Tourdes says that it is most prevalent in the spring and fall. Gierke observed it throughout the year, but more in the winter, while Mayr says that the season is without influence. In Woronichin's series of 22 cases, about as many occurred in the summer as in the winter. The greater prevalence of epidemics

of measles during the winter, may serve to account for the larger proportion of cases occurring at that season.

Pathological influences.—All writers agree upon the important predisposing part played by chronic and acute diseases. Baron says that gangrene of the mouth is never primary, but occurs in children weakened by a former disease. Barthez and Rilliet agree with this entirely. It has been observed in connection with, or as a sequel of, measles, scarlatina, variola, pneumonia, pertussis, intestinal diseases, intermittent fever, diphtheria, typhoid fever, syphilis, varicella, erysipelas, rhachitis, hemophilia, tuberculosis, pulmonary gangrene, bronchial catarrh, and amebic dysentery. Tourdes analyzed 98 cases observed by various authors and found the order of frequency of the different diseases to be as follows:

Measles	39	Pulmonary tuberculosis	3
Intermittent fever	8	Pneumonia	2
Typhoid fever	7	Dysentery	2
Mercurialism	7	Scurvy	2
Pertussis	6	Syphilis	2
Scarlatina	5	Bronchitis	1
Variola	5	Diphtheria	1
Enteritis	5	Cerebral congestion	1
Scrofula	4		

Of these predisposing diseases measles stands pre-eminently first. Osler claims that at least one-half of the cases develop during the convalescence from measles. Krahn records 33 out of 133 cases following measles. Bouley and Caillault found measles was the antecedent in 41 out of 46 cases. Allbutt places typhoid fever in the second place. Carrière-Montjosieu reports 11 cases of noma following typhoid fever and says it is not a rare complication. Keen (quoted by Sailer) found noma recorded in nine out of 1,700 cases of typhoid fever with surgical complications. Cases following scarlatina are uncommon. Tourdes recorded only five out of 98 cases, and Woronichin only four out of 22 cases. The case referred to in this article followed this disease.

Taupin believed that there was almost an antagonism between noma and tuberculosis, but this was not proved by autopsies done later by Barthez and Rilliet. Barthez and Rilliet say that noma rarely occurs in cases of extreme tuberculosis, but in nine out of 20 sections upon noma cases they found slight tuberculosis lesions, which led them to assume a connection between gangrene and the after-products of the tubercle.

The evidence that scurvy was a great etiological factor in noma, as was believed by the ancient physicians, was much exaggerated, according to Tourdes, who says it has not been found by modern observers to be associated with this disease.

According to Perthes (1902) noma is associated with splenic tumor developing after malaria.

Therapeutic influences.—It was formerly supposed that calomel had much to do with the causation of the disease. Dieffenbach and Simon, cited by Tourdes, affirm positively to having seen noma follow large doses of calomel. Gierke and Mayr think it may favor the occurrence of noma in a few cases, but they, as well as Coates and West, deny that it plays any considerable rôle.

Contagiousness.—There are few or no examples of well-authenticated contagion, although a few instances are at least very suggestive. Bruns refers to an instance observed by Lund in which a case developed in a room in which a sister had died of the same disease; and to an observation by Siebert, in which two sisters and two

other patients were attacked in the same house. Mayr believed in the contagiousness of noma and insisted on isolation. Holt considers there is little doubt as to the contagiousness of noma. He observed five cases, following whooping-cough, develop in a single ward, all beginning in the auditory canal. They were apparently produced by using the same syringe which had not been properly disinfected. Most writers have denied the occurrence of contagion, and have shown that it did not occur even when abundant opportunity was presented. The question must be considered unsettled, but with the present tendency to ascribe to certain bacteria the etiological rôle, the possibility of direct transfer becomes most important, and even if certain saprophytic bacteria are the active factors, in their condition of heightened virulence they may be better able to infect other persons than when in their normal condition.

Epidemics of noma have been described. Barthez and Rilliet never observed an epidemic. Bouchut says that it sometimes occurs epidemically. The occurrence of epidemics, like that of contagion, is doubted by most writers. Blumer and MacFarlane in 1901 reported an epidemic of noma in the Albany Orphan Asylum, during which 16 cases developed among 173 children who had suffered from measles during a severe institutional epidemic. The type of the measles was severe, often accompanied by complications. Of the 16 cases reported, all occurred in the girls' dormitory, except two cases in boys in the infirmary, where cases of gangrene were being treated. Although there were nearly twice as many cases of measles among the boys as among the girls, no case of noma developed in their dormitory. After the cases were thoroughly isolated no new cases developed.

Bacteriology.—The bacterial study of noma has always been conducted with certain difficulties, one being the rarity of the disease, so that a series of cases have not come under the observation of any one investigator within a reasonably short time; another being the large number of bacteria found in the gangrenous tissue, some of which cannot be grown by aerobic methods or upon the nutrient media usually employed; and a third being the difficulty of producing a corresponding disease in experimental animals.

There are two varieties of organisms which must be considered as having been shown to be associated with the disease by several independent investigators; the anaerobic, threadlike organism first cultivated by Seiffert, and the diphtheria bacillus.

The threadlike organism, which was first cultivated by Seiffert in 1897, was undoubtedly observed in nomatous tissues before that time. Lingard in 1888 described long, threadlike growths which were found in great numbers at the line of the extension of the necrotic patch. He did not cultivate it nor describe its staining properties. Grawitz in 1890, in a single case, observed bacilli at the junction of the necrotic and healthy tissue, which grew into long threads. No cultures were made. The organisms stained by Gram's method. Bartels in 1892 examined microscopically material long preserved in alcohol from two cases. Deep in the necrotic tissue he found innumerable long, slim bacilli, often appearing as threads. They were most numerous near the demarkation zone, and passed with the loose connective tissue from the necrotic tissue into the infiltrated zone. They stained by Loeffler's method, while the staining by Gram's or Weigert's methods was not always successful. He demonstrated by special stains that the threads were not elastic tissue. Foote in 1893 studied a case in a girl of seven years, in whom whooping-cough followed by typhoid fever had prepared the soil for noma. Along the border of the necrotic zone a bacillus which was often seen in long strings was present in preponderating numbers. It

was not confined to the necrotic area, but had also infiltrated the sound tissue in smaller numbers. It is said to have stained by Gram's method, but that great care was necessary to avoid decolorizing too much. In the older necrotic tissues a variety of cocci were present.

Elder in 1893 studied a case in a girl of four and one-half years, following measles. Aerobic cultures removed soon after death remained negative. In sections long, thin bacilli, tapering at the ends and commonly in pairs, were seen around the vessels and extending outward into the tissue. They were well seen passing between the fat cells of the tissues of the cheek. The organism stained pretty well by Gram's methods but were readily decolorized by clove oil.

Seiffert in 1897 studied two cases of noma, and by means of anaerobic cultures he obtained a cladothrix, which he believed to cause gangrene. The cultures produced a progressive necrosis in guinea-pigs which eventually terminated in suppuration. Suppuration was also produced in rabbits. He was apparently the first one to cultivate this organism.

Schmidt in 1898 studied a case in a child of 7 years. In the boundary zone and in the necrotic tissue were found abundant, delicate bacilli with rounded ends. They were observed to follow the connective tissue into the healthy tissue, and were especially abundant in vessels lying within the necrotic area. In many places were seen bent, delicate threads, apparently consisting of the same bacilli.

Perthes in 1899 studied two cases. In sections of the tissues which were stained 24 hours in carbol-fuchsin and decolorized with 70 per cent alcohol, he found what he designates as a streptothrix. In the necrotic tissue were seen threaded structures in great abundance. The caliber of the threads was variable, the larger being recognized as composed of a line of bacilli, the finest appearing more homogeneous and many winding over the greater part of the field. Some threads exhibited spindle-shaped enlargements. Among the threads were found rods of varying length and many spindle-like elements of varying dimensions. As the living tissue was approached the threads became more rare and the finer ones correspondingly numerous, lying often in thick bundles or tongues and following the direction of the still distinct tissue fibers. The nearer the sound tissue was approached the more the field filled with threads of extreme fineness. Beyond the border of the necrotic tissue in the sound tissue isolated threads were observed lying between the living cells. Here spiral forms were observed. If Weigert's stain was employed, only the larger threads were stained, and even in these, parts did not retain the stain. In teased preparations from the border zone some threads were seen to exhibit dichotomous branching, and strongly bent "spirilla" were also seen. The author believes that the various forms observed in the border zone belong to one variety of bacterium.

In deep agar cultures (anaerobic) a cloudlike growth occurred about the fragments. This growth was always mixed, but contained threads closely resembling those in the tissues, both in form and staining properties. Pure cultures could not be obtained. Because the organism is most abundant in the necrotic tissues, and because it is found among the sound tissue elements, he believed it to be the cause of the disease.

In 1902 Perthes reported the frequent occurrence of noma in the Chinese, associated with the splenic tumor of malaria. In these cases he found the same bacteria the had previously reported in cases in Germany. He insists that "spirilla" are erminal enlargements or stages in the development of fusiform bacilli.

Krahn, in 1900, described in the tissues of a case of noma threads corresponding to those observed by Perthes. He was unable to observe branching, and because of this, and because of the fact that threads were sometimes made up of distinct links, he concluded that the organism was not a streptothrix. The threadlike organisms were not cultivated. His idea is that noma is due to a mixed infection by various mouth bacteria, especially with the "*Spirillum sputigenum*" and "*Spirochaetae dentium*."

Blumer and MacFarlane in 1901 reported a most interesting epidemic of noma, in which 16 cases of noma occurred among 173 cases of measles. In all cases a threadlike organism was present in cover-slip preparations. It stained best with carbol-fuchsin, and stained faintly by Gram's method. In sections it was best seen after staining with carbol-fuchsin and decolorizing in oil of cloves according to Flexner's method. In such sections in the deeper part of the necrotic zone the organism was present in enormous numbers. The individual bacteria were nearly always seen as long threads, which for the most part lay parallel and between the connective tissue fibrillae. The organisms were fewer in the zone of reaction, and a small number were found in apparently unaltered tissue. Efforts to cultivate the organism failed.

Seiffert in 1901 reported the study of four additional cases, in all of which he was able by anaerobic methods to cultivate the same threads, "spirilla," and branching forms of cladothrix as in the earlier cases. By animal experiments he showed his cultures to be pathogenic for guinea-pigs and rabbits, and he observed a spontaneous contact-infection of the lip of a rabbit.

Braun, in 1901, in discussing Seiffert's presentation, referred to a case of noma in which he had found the thread organism described by Seiffert, but efforts to cultivate it anaerobically or transfer it to animals were futile.

In 1902 Matzenauer published a paper upon noma and hospital gangrene in which he attempted to show that the two diseases are identical clinically and bacteriologically. In the nomatous tissues he described, in the border zone, a great number of bacilli of uniform shape, in entangled heaps, staining intensely and uniformly by Weigert's stain. The bacilli were slender, straight, or slightly curved, usually single, often in pairs end to end. The ends were usually not angular but slightly rounded. If the process was progressive the bacilli were deep in the tissues where there was no necrosis or even marked inflammatory reaction, and only fibrin network was present about the vessels. The bacillus is said to be anaerobic, but no details are given as to the cultures. He believes these bacilli are the same as observed by most former authors in cases of noma, and apparently identical with the bacilli observed by Vincent and himself in hospital gangrene.

In 1903 Ranke was ready to declare his conviction that noma was caused by a fungus, closely related to actinomyces. The threads did not stain by Gram's method.

Rosenberger in 1904 reported some observations in a child with noma of the cheek. In smears from the margin nearest the mouth there were various bacteria. Most abundant were "spirilla" and bacilli arranged in pairs, the distal ends being pointed. Cultivation of these bacteria was not accomplished.

Brüning in 1904 described in sections of nomatous tissue, thick tangles of filaments, but in his illustrations he figures only individual bacilli. He was able to grow the same organism as described by Seiffert in anaerobic cultures in bouillon and agar.

Hofmann in 1904 found, in a case of noma, bacilli in the freshly infiltrated part

as well as in the necrotic portions. They were five micra in length, straight or comma-shaped, and were sometimes swollen in the center. Threads two or three times as long were also observed without regard to location. They showed spirils, but never more than two. "Spirilla" were observed in the necrotic tissue. Both the bacilli and "spirilla" were seen in the subcutaneous fatty tissue. The spirilla were similar to those found in the mouth. In the deepest necrotic portion he found other bacteria. The best pictures were obtained when Weigert's modification of Gram's stain was used. If Gram's method was used care must be made in differentiation. The spirilla were stained best by carbol-fuchsin used for 24 hours. The author did not believe that the bacillus was a part of the mycelium-forming organism.

Rona in 1905 reported three cases of noma, two following measles. In all of the cases fusiform bacilli appeared to play an important rôle. In one case "spirochaete" were associated with the bacilli, the two organisms being found in pure culture at the border of the necrotic tissue. In one case a few "streptothricen" were seen in the necrotic tissue. In the deep tissue only the bacilli were present and they were in enormous numbers.

Buday in 1905 found in two cases of noma many different kinds of bacteria in the necrotic tissue. On the surface were cocci, diphtheria-like bacilli, colon bacilli, "spirilla," long threads, and fusiform bacilli. In the deeper parts filaments were seen in enormous numbers. Nearer the border of the necrosis thick groups of fusiform bacilli were seen. Here comma-shaped bacilli were also observed. At the border of the necrotic tissue and in the living tissue spirilla were observed in large numbers. He does not consider the fusiform bacillus and spirillum to be different forms of one organism. He found carbol-fuchsin best for staining the spirochaetae, using it for from six to 24 hours. The fusiform bacilli held Gram's stain quite long. The bacilli stained by Weigert's modification of Gram's method. He concludes that mouth and pharyngeal gangrene are due to different kinds of mouth bacteria, especially the symbiosis of a spirillum and a fusiform bacillus.

Pollard in 1905 found fusiform bacilli and "spirochaetae" in three cases of nosocomial gangrene in ulcers on the leg. He considers the fusiform bacilli the exciting agent and the spirochaetae simply saprophytes.

Herrman believes that the organisms called by him "spirochaetae" of necrosis, corresponding to the streptothrix of Seiffert and Perthes play the most important part in the etiology of noma. He considers that this organism is identical with that found by Plaut, Bernheim, Vincent, and others in ulceromembranous lesion of the mouth and with the *Spirillum sputigenum* and the *Spirochaete dentium* of Miller found normally in the mouth. He believes that they are different stages in the development of the same organism, and that this organism is not a bacillus but belongs to the family of spirochaetae.

Herrman calls attention to the fact that gangrenous processes similar to noma have been observed in lower animals. According to Roux the *Bacillus necrophorus* (Flügge) is identical with the *Bacillus diphtheriae vibulorum* (Loeffler), necrose bacillus (Bang), *Bacillus necroseos* (Salmonsen), *Streptothrix cuniculi* (Gasperini), *Actinomyces necrophorus* (Nuekirsch), and *Streptothrix necrophora*. Jensen calls this organism the *Bacillus necroseos* or the bacillus of necrosis.

According to Herrman this organism occurs in necrotic processes in the horse, cow, pig, kangaroo, ape, stag, antelope, and rabbit. Guinea-pigs, cats, and pigeons appear to be immune. This author describes the organisms as occurring in the form

of slender, straight, or curved rods. Several may be joined end-to-end, forming threadlike structures, and finer filaments are also seen. Schmorl also observed micrococcus-like bodies which, according to Herrman, may represent a stage in the development of new organisms. The organisms stain moderately well with carbol-fuchsin and carbol-thionine. Some show interrupted staining, some deeply stained, round bodies. The organism is an anaerobe, growing best in serum and blood-serum agar. The organisms are found penetrating apparently healthy tissue beneath the necrotic area in which they do not thrive.

From the similarity in the clinical, bacteriologic, and histologic characteristics Herrman thinks it probable that these necrotic processes in animals are analogous to noma in human beings, and that the organisms present in both are closely related.

Several of the observers just cited obtained a variety of bacteria, including cocci (staphylococci and streptococci) and pseudodiphtheria bacilli, from the tissues which had been dead for some time. Whether all these authors really described the same organism is doubtful. The various statements regarding the reaction exhibited to Gram's and Wiegert's stain are confusing. The fine threads described by Seiffert and Perthes and some of the later writers stain very faintly by Gram's method and are decolorized if care is not taken to avoid it. In this connection it must be remembered that, for purposes of differentiation, little dependence can be placed upon statements as to the staining or non-staining of a bacterium by Gram's method. The final result will vary with the thickness of the preparation, the composition of the staining fluid, the time the stain is allowed to act, and the degree to which the decolorization is carried. Partial decolorization becomes complete decolorization if the process is prolonged a little. The danger of depending upon Gram's stain for the differentiation of bacteria in sections of tissues is greater than in fresh smear preparations, because of alterations in the staining properties produced by various fixing and hardening agents.

That the delicate threadlike organism of Seiffert has sometimes been overlooked or mistaken for delicate connective tissue remnants is most probable, because of the faintness and difficulty with which it is stained. Bartels was at first in doubt whether the threads in his sections were not elastic fibers, but demonstrated that they were not by the absence of characteristic staining reaction.

From the study of the case of facial noma herein reported, the authors believe the organisms observed in the sections at the line of advancing necrosis are the threaded and spiral forms of one organism. The forms observed in the tissues correspond with the forms shown by us to occur in pure cultures of fusiform bacilli. These organisms have been described in previous articles (see Bibliography).*

The other organism which has been observed in connection with noma is the diphtheria bacillus. The first mention of the presence of the diphtheria bacillus in connection with noma was made by Bishop and Ryan in 1895. In the case reported by them, the bacteriologic examination was made by one of us (Weaver), and a diphtheria bacillus with little virulence for guinea-pigs was isolated in pure culture from the deepest part of the diseased tissue. No anaerobic cultures were made. No delicate threads were observed, but may have been present and overlooked.

* One of us (Tunnicliff) has been criticized by Mühlens (*Deutsch. med. Wchnschr.*, 1906, 20, p. 797), for not distinguishing between "Spirilla" and "Spirochaetae." At this time knowledge of these organisms is too limited to warrant an attack upon the use of terms which have both been applied by various authors to apparently the same organisms.

In 1896 Nicolaysen described in two cases a polymorphous bacillus, staining by Gram's method, and resembling the diphtheria bacillus, but possessing no pathogenic properties.

Saft, in 1898, cultivated from one case a bacillus which he describes as diphtheria-like.

Petruschky and Freymuth in 1898 reported a case of genital noma in a girl of three years, following measles. Smears from the necrotic surface contained various kinds of bacteria, among them some which resembled diphtheria bacilli. Two injections of antitoxin were given, 2,500 units in all. Recovery began soon after the second injection. By means of cultures diphtheria bacilli which were not highly virulent for guinea-pigs were isolated. Microscopic examination of the necrotic tissue gave a relatively limited number of typical diphtheria bacilli, and a large number of vibriones, bacilli, and fine spirilla.

Later in the year they reported a case of moderate gangrenous stomatitis in a boy of eight years following typhoid fever, from which a diphtheria bacillus was cultivated which was slightly pathogenic for guinea-pigs. Microscopically abundant spirilla and bent bacilli were found, corresponding to those of Bernheim, Miller, and Abel. The child recovered after receiving diphtheria antitoxin.

Passini and Leiner in 1899 reported a case of extensive noma in an eight-year-old tuberculous child, coming on without any acute disease. Preparations from the superficial parts contained long bacilli with pointed ends, resembling those described by Bernheim and others in stomatitis. In the deeper parts of the gangrenous tissue and at the border of the sound tissue, in smears and cultures they found diphtheria bacilli in pure culture. The diphtheria bacilli were pathogenic for guinea-pig and diphtheria antitoxin protected the animal against them.

Walsh in 1901 reported a series of eight cases of noma, occurring in St. Vincent's Home in Philadelphia, most of them following measles. From all of them he cultivated true diphtheria bacilli, which were shown to be virulent for animals. He considers the diphtheria bacillus as only one cause for noma.

Sailer in 1902 reported two cases of typhoid fever complicated by noma, from both of which diphtheria bacilli were cultivated. Guinea-pigs into which the cultures were injected were made sick for a few days, but recovered.

Other observers have found diphtheria bacilli associated with noma without concluding that they were the cause of the gangrene. Among such are Guizzeth, Hofmann and Küster, and Verhoeff.

In view of more recent studies of the pseudodiphtheria bacilli, it is not unlikely that some of the bacteria reported as diphtheria bacilli were really pseudodiphtheria bacilli. This is more probable as in most instances the bacteria were said to possess very slight virulence. In this connection it may be noted that E. H. Ruediger has found pseudodiphtheria bacilli associated with gangrenous anginas of scarlatina which are virulent for guinea-pigs.

The two varieties of bacteria already discussed are the only ones which have been found by any numbers of observers. Other bacteria have been encountered by a single or a few observers.

Froriep, *Chirurg. Kupfertafeln*, 1844, Taf. 438, 39, appears to have been the first author who attempted to demonstrate a causal relationship between vegetable organisms and noma. In sections from a rapidly fatal case he pictured small, round structures lying between muscle fibers and connective-tissue cells.

In 1872, Strueh studied the necrotic tissues from a case in an adult and found what he believed to be the same organisms as pictured by Froriep, which he described as rather thick and double-contoured. They were associated with leptothrix and he designates them as "nomapilz."

Babes and Zambilovici in 1892–93 found in two cases of noma a slender aerobic liquefying bacillus, which grew well on most media and did not stain by Gram's method. It caused gangrene in the cheeks of rabbits. They considered it the cause of the gangrene, although they also described abundant, undulating, and ramifying filaments resembling actinomyces in the tissue. Guizzetti in 1896 found the same bacillus in one case, which produced gangrene and abscesses in experimental animals.

Schimmelbusch in 1889 described an aerobic bacillus which he cultivated from a single case. It grew readily on all kinds of media, and produced necrosis and abscesses in experimental animals.

Longo in 1903 cultivated from a case of noma an aerobic bacillus, which corresponded in most respects to the one described by Babes and Zambilovici.

Hofmann and Küster in 1904 isolated a sporulating aerobic bacillus from a case of noma which they believed to be etiologically connected with the disease.

Some writers have been inclined to consider the streptococcus the most important factor in the causation of noma, among them being Ranke, Holt, and Verhoeff.

Almost everyone who has made bacteriologic studies of noma, has found a great variety of organisms in the older gangrenous tissues. Because of this and because of the lack of uniformity in results, many have concluded that noma is due to the combined action of bacteria from the mouth acting upon specially vulnerable tissues. In this group are Baumgarten, Comba, Durante, Trambusti, and Strada. Rosenbach compares this infection to that of tetanus, malignant edema, and rauschbrand, in which saprophytes under favorable conditions invade the tissues.

The organisms observed in the nomatous tissues at the line of advancing necrosis appear to resemble very closely certain bacteria found in the mouth under diseased and normal conditions. Attention has been called to this by Herrman, Rona, Buday, and others. Further study must determine what relation the bacteria found in the tissues bear to the necrosis, and in what they differ from normal oral bacteria if they really do so differ. According to Rona, 1905, gangrenous, diphtheritic phagedenic chancre is a local infection similar to gangrene in which "spirilla" and bacilli are present on the surface and the bacilli alone in the deeper tissues. He considers that Vincent's angina, ulcerous stomatitis, gangrenous stomatitis, and noma must be considered identical, differing only in degree, on account of the similarity of their location, clinical course and pathological anatomy, their character and histological structure, and the morphological and staining properties of the bacteria. He thinks that the spirilla and bacilli cannot be differentiated from Vincent's organisms found in hospital gangrene. The same organisms were found by him in pulmonary gangrene. He believes that ulcerous stomatitis and mercurial gangrene differ from each other only in that in the latter mercury causes the lower resistance. He considers Miller's organisms found in the mouth to be the same as the ones found in all these various conditions. He says that the clinical, anatomical, and bacteriological similarity make one think of a common etiology, but that this must be determined by cultures and animal experiments.

Buday, from the study of cases of noma, gangrenous pharyngitis, gingivitis, and stomatitis, believes them to be different types of the same process. He found the patho-

logical anatomy and bacteriology to be the same. He considers that these lesions are due to different kinds of mouth bacteria, especially the symbiosis of a spirillum and fusiform bacillus.

Rona calls attention to the fact that noma of the face begins without exception in gangrenous stomatitis. If the fusiform bacilli or spirilla found in the mouth are etiological factors in the gangrenous stomatitis, as these organisms are found in such abundance in the tissue of noma cases, it would seem probable that the organisms are the same. Since in all of these conditions, lowered resistance plays such an important rôle, he believes that under such conditions these saprophytic mouth bacteria may become virulent.

PATHOLOGICAL ANATOMY.

The gangrene is most often observed to involve the tissues about the mouth and those about the genito-anal region. In girls the genital gangrene comprises quite a large percentage of the cases. The conditions which favor the peculiar form of infection seem to be furnished by both locations. The primary gangrene may also involve the tissues of the external ear. The gangrene may be limited to any one of these locations, or may appear simultaneously or consecutively in two or more.

Of 16 cases observed by Blumer and MacFarlane, the mouth was alone involved in four; the mouth and other parts, i. e., ear and vulva, in three; the vulva alone in two. In three cases the rectum alone was affected and in five the rectum was involved together with other parts. The frequent association of gangrene of the face with that of the external genitals has been remarked by Blumer and MacFarlane, Bouchut, Orth, and Richter. Gangrene of the external genitalia alone has been noted by Blumer and MacFarlane, Gierke, Mayr, and Wood.

Among those speaking of gangrene of the rectum alone or combined with a similar lesion elsewhere, are Blumer and MacFarlane and Bouchut. Gangrene of the tissues in the region of the external ear have been spoken of by Blumer and MacFarlane, Gierke, Holt, and Mayr.

According to Tourdes, Taupin observed gangrene of the lungs, pharynx, esophagus, and stomach, in eight out of 36 cases. Barthez and Rilliet, out of 20 cases found gangrene of the lungs and pharynx four times.

Tourdes says that the gangrene occupies most often the middle of the cheek, next in frequency the lips, especially the lower. It can destroy half the face, the neck, eyelids, forehead, and the nose. Less often it attacks the arch of the palate, especially the posterior part, the uvula, the tongue, and the floor of the mouth. It is unusual for both sides of the face to be affected at the same time. Some statistics seem to show that the left side is more often involved than the right.

In the following description as in other places the excellent work by Barthez and Rilliet, based upon examination of 20 cases, has been largely utilized.

Skin.—In fatal cases of noma there is more or less involvement of the skin which lies over the deeper tissues affected. The cheek or lip is swollen, violet or greenish, tense and shining as if oiled. Over the highest part of the swelling there is often seen a circular or oval, regularly outlined, gangrenous eschar, varying from 1 cm. to 3 cm. or so in diameter. In other cases the sequestrum is larger, involving irregularly varying parts of the face, and extending to the chin, neck, nose, eyelid, and even as far as the ear. Half or even almost the whole face may be involved. The eschar is always black, and usually is dry like parchment. It may extend only 1 to 2 mm.

into the skin, or entirely through it, and rarely ever involves the underlying tissues. After the sequestrum has separated there remains a perforation of the soft parts, revealing the deeper parts and even the interior of the buccal cavity.

Mucous membrane.—When the cutaneous surface has undergone gangrene, there is always involvement of the mucous membrane. It may, as in the skin, be limited and appear as an ulcer with a grayish-black base, lying in the fold between the cheek and gum, or upon the cheek opposite the space between the rows of teeth. On the other hand, the destruction of the mucous membrane may be extensive, extending from the angle of the mouth back to the soft palate. There is destruction of the mucous membrane through its entire thickness, the surface presenting a black or brown semi-fluid mass which is readily scraped away and contains structureless fragments of the necrotic mucous membrane. There is usually partial or complete destruction of the gums on the corresponding side.

Jaw-bones and teeth.—With gangrene of the gums the teeth are loose and easily extracted or have already fallen out. Incisors, canines, or molars may be affected. With the destruction of the periosteum the jaw becomes denuded and necrotic, and fragments may be loosened.

Tissues between the skin and mucous membrane.—In the simplest condition the fatty tissues and muscles of the cheek are infiltrated with serum, but still retain their structure and form a firm mass deep in the cheek. If the process is more severe or advanced, gangrenous changes are also observed in the deeper structures, especially where they approach the affected skin and mucous membrane, and thus a brownish putrifying mass, 5–8 mm. thick, is seen, beyond which the fatty tissues and muscles are infiltrated with serum, appearing homogeneous and structureless. Rarely the entire thickness of the cheek or lip appears gangrenous, and if the slough has separated a perforation is observed.

Vessels and nerves.—In the tissues which are only infiltrated the vessels are permeable and their walls scarcely at all thickened. At the border of the gangrenous tissue the vessel walls are thickened and begin to have the appearance of gangrenous tissues. In the interior of the gangrenous tissues the vessels can still be followed, but their lumina are closed by coagula. The coagulum stops abruptly at the limit of the gangrenous tissues. Sometimes a gangrenous mass is found within an artery. The veins may contain an ichorous material. Nerves were examined once and in the middle of the gangrenous area they had the external appearance of the surrounding tissues. On section the "Nerven-mark" appeared normal. The ductus of Stenson was examined once and was found permeable throughout, and opened freely in the center of a gangrenous remnant of mucous membrane.

In gangrene of the vulva, the lesions are similar to those observed in the cases in which the face is involved. Tissue destruction may be extensive and extend to the structures about the rectum.

MICROSCOPIC ANATOMY.

The microscopic appearances presented by nomatous tissues have been described more or less in detail by a number of authors during the past 15 years. The following is based upon the descriptions of Bartels, Bishop and Ryan, Blumer and MacFarlane, Foote, Krahn, Kraus, LeCount, Matzenauer, Perthes, Schimmelbusch Schmidt, and Verhoeff. All these descriptions accord in the main. Schimmelbusch characterized noma as an acute mortification of tissue without reaction of neigh-

boring tissues worthy of notice. A sharp line of demarkation between the living and necrotic tissues is mentioned by most writers. Several authors speak of three distinct zones: (1) necrotic; (2) middle zone of infiltration with round cells; (3) normal tissues. The degree of infiltration in the middle zone has presented great variation in different cases, from the extreme cases of Verhoeff in which there was no inflammatory reaction, to those in which infiltration is described as extensive. Others say that the small cell infiltration is slight. In general it would seem that the degree of infiltration is largely dependent upon the rapidity with which the gangrene is advancing at the point examined, the accumulation being absent or very limited when the gangrene is progressing rapidly, and being abundant when the necrosis is at a standstill or making little headway. In the transitional zone, between the tissues which are necrotic and those which are the seat of inflammatory reaction, Matzenauer describes a wall consisting of a network of fibrin. Fibrin masses are often found deep in the tissues about the vessels which are dilated and distended with blood. The walls of the vessels in the inflammatory zone early present the appearance of coagulation necrosis, and, in preparations stained by Weigert's method, are surrounded by an intensely staining network of fibrin. Schmidt says that near the boundary zone there is marked intermuscular edema, the muscle fibers presenting a swollen appearance. The nuclei of connective tissue and muscle cells are the first to exhibit degenerative changes. The mucous glands appear most resistant.

The zone of necrotic tissue takes a diffuse stain, the structural outlines of muscle, glands, and other structures being often preserved, but all are lacking in nuclei which stain. There are also altered blood cells and fibrin. In the necrotic zone are seen many strands of elastic connective tissue which seem to be most resistant to the necrotic process. Bartels described mast-cells in the zones of necrosis and inflammatory reaction. He also says that in one case the nerve fibers in the necrotic parts were almost unaltered.

SYMPTOMS.

According to Tourdes and other observers there are usually no constitutional symptoms until the gangrene is well established. After the disease has existed for several days symptoms of marked prostration and sepsis develop, sometimes quite rapidly (Holt). As a rule the patient is suffering or convalescing from some severe disease so that the symptoms are masked by those accompanying the primary trouble.

Face.—It is usually pale at the onset and remains so during the entire course. In the cases observed by Barthez and Rilliet, the face became somewhat red during the last day of the illness in one case, and yellowish in another. The parts unaffected by the gangrene are often marmolated violet. There is often an edema of the eyelids, but if it is absent the eyes are sunken. The lips are covered with crusts. The alae nasi are usually dilated. The nose is pointed, when not involved in the gangrene. The parts affected loose all expression.

General expression.—The patient is usually quiet and woeful, often languid and peevish, sometimes very fretful and ill-natured. Rarely the child remains in good spirits. The appearance is often that of a cachectic or acute secondary disease.

Strength and position.—Baron always found prostration of strength; in the case of Destries the strength was maintained throughout the course of the disease. Some children are completely prostrated, others suffer little from loss of strength and sit up in bed, interested in their surroundings to the last day. One case of Barthez and

Rilliet got out of bed unassisted the day before death. Destries' child played cards when the gangrene was at its height. The children showing great prostration have usually been greatly weakened by some preceding disease.

Pulse.—It is usually said to be frequent and very small. The character depends largely upon the accompanying conditions. In some cases in which gangrene was the chief disease, Barthez and Rilliet noted that at the onset there was slight increase in the frequency of the pulse, being 80 to 100 or 120, and that it never exceeded this even in very young children, but always toward the end became small and imperceptible. In cases appearing in the course of other acute or chronic diseases the pulse was observed to become more rapid soon after the gangrene began, reaching 120 to 140.

Fever.—According to Tourdes there is no fever as a rule, even in very young children, unless there are complications. In some the skin is hot and feverish, in others cool or cold. The difference depends upon the accompanying disease. Gierke found the fever to be variable. According to Holt the temperature is usually elevated to 102°–103° F., sometimes rising to 104°–105° F. He says it may become subnormal before death.

Sweats.—The skin is always dry rather than moist. According to Tourdes viscid perspiration has been observed, probably an agonal phenomenon.

Anasarca is rare. Bartels found in a woman 40 years of age general edema as death approached.

Digestive system.—Children usually retain their appetite and even desire to eat to the last moment. In a case of Barthez and Rilliet, the appetite had been partly lost from another disease, but improved with the onset and during the course of the gangrene. Thirst is usually marked, and patients drink greedily. The tongue is always moist, sometimes yellowish, rarely red. In some instances it becomes black on the affected side from involvement in the gangrene. In the cases observed by Barthez and Rilliet, vomiting was never observed, but diarrhea was always present. In a case of a woman 40 years of age, observed by Bartels, there was diarrhea toward the end. Gierke usually but not always found diarrhea present. It occurs when the gangrenous tissue breaks down, and is probably due to swallowing fragments of the tissue. Of the eight cases of noma of the genitalia and external ear observed by Gierke, slight diarrhea of short duration occurred in only one.

Respiratory system.—Frequently pneumonia, most often broncho-pneumonia, occurs as a complication.

Nervous system.—Barthez and Rilliet never observed nervous symptoms. In the case of Destries and in several of those of Baron, sleeplessness and delirium were present. Gierke says that a few days before death all children become restless, later apathetic, and die in a state of exhaustion. Delirium was present in none of Gierke's cases.

Renal symptoms.—Bartels reports slight albuminuria in a woman 40 years old.

PHYSICAL SIGNS.

I. FACIAL GANGRENE.

The mucous membrane, the deep tissues, and the skin have been considered as sites for the first appearance of this disease.

The gangrene almost always begins in the mucous membrane. This was found

to be true in all cases observed at the beginning by Barthez and Rilliet, and their observations accord with those of Destriel, Baron, Tourdes, Bouley, and Caillault. Bartels reports a case in a child three years old in which the necrosis began on the left tonsil and extended to the palate and pharynx. Bouchut believes that aphtha, which has become gangrenous, is always the source of the gangrene which involves the cheek. Brüning reports four cases of which two developed from an ulcerative stomatitis and two seemed to begin in an ulceration of the hard palate. Coates thinks that the disease generally starts at the edge of the gums. He never saw a case begin on the inside of the cheek. Filatov considers that noma generally develops from "stomacace." Henoch believes that it almost always begins in ulcerative stomatitis. Mayr in 14 cases after measles observed it to develop seven times from "stomacace" and "nymphacace," once from an excised "abscesse excarié," five times from gangrenous vesicles upon the inner side of the cheek, and once from an eczematous inflammation of the external ear. Bohn observed the gangrene to develop from a stomatitis. According to Allbutt it occasionally follows ordinary ulcerative stomatitis.

A. L. Richter, Delaberge, and Mouneret and Billard all agree that the first sign of the disease is often a hard, indolent swelling of the size of an almond, lying deeply in the tissues and accompanied by some redness. Taupin, Gierke, and Henoch also believe that gangrene may begin in the deep tissues of the cheek. Tourdes thinks if gangrene ever does originate here, it is exceptional. Barthez and Rilliet know of but one well-authenticated case, that of Key.

Weber, quoted by Tourdes, observed a case in which the gangrene began in the skin. Bohn (1880) says that there are no authentic cases in which noma originated in the cutaneous surface of the cheek. Kraus (1902) quotes Bainbridge as finding two cases out of 100 which developed from without. Filatov (1904) says "noma sometimes begins with the skin of the cheek."

Barthez and Rilliet from their own experience and that of others conclude that gangrene may begin in three ways:

1. Most often with ulceration followed by gangrene of the mucous membrane.
2. With an edematous swelling followed by gangrene of the mucous membrane.
3. Gangrene of the deeper parts, extending later to the mucous membrane and skin.

Mucous membrane.—Baron and Destries always observed upon the mucous membrane first a small aphtha or phyctena, which later enlarged. Barthez and Rilliet observed on the first day an ulcer upon the mucous membrane similar to that of stomatitis, either on the alveolar border of the gums, in the gingivo-buccal fold, or on the central part of the cheek opposite the space between the rows of teeth. This ulcer was sometimes very small, a few millimeters in extent, with a gray or a distinctly gangrenous covering.

Bouley and Caillault claimed the ulcer was always gangrenous from the first day, but this is certainly not in accord with the observations of other writers. Sometimes the ulcer remains a long time and forms a true stomatitis which passes through its phases and terminates with gangrene. This has been observed by Barthez and Rilliet.

When gangrene has once begun, the ulcers spread quite rapidly; they bleed readily, become gray, then black and covered with a fluid ichor. The extension of the gangrenous process is more or less rapid, and in from three to 16 days may involve the entire mucous membrane of the affected side. Later the gangrenous parts become

detached in fragments, and fall into the mouth, or are pulled off by the child without pain.

Teeth and jaw-bones.—With the gangrenous destruction of the gums the teeth become loosened and fall out. The jaw, denuded of its periosteum, becomes necrotic to a corresponding extent. If life is sufficiently long preserved, or if recovery takes place, necrotic fragments of jaw may separate and be discharged. Such fragments may carry teeth with them. The necrosis may extend beyond the jaw-bone to the malar, temporal, and orbital bones.

Salivation.—There is usually a profuse flow of saliva, which early is sanguinated, and soon becomes black or brown with the gangrenous fragments in suspension.

Odor.—The odor from the mouth is very offensive and characteristic. The breath is usually fetid from the first few days, sometimes even before one notices a change in the buccal mucous membrane. It is often the first thing to excite attention. Of itself the odor is not enough upon which to base a diagnosis, as pseudo-membranous stomatitis may emit a very similar odor. Henoch says that the odor is not only fetid, but gangrenous, and may not be detected readily.

Skin and underlying tissues.—There may be an edematous swelling of the lips and cheek before the gangrene appears, which is like that observed in ulcerative stomatitis. This is usually present one or two days before the hard central swelling appears.

Swelling of the submaxillary glands.—Taupin, quoted by Tourdes, observed an enlargement of the submaxillary glands in four cases out of 36. Boeckel and Constant also encountered it (Tourdes). Most of the earlier physicians have not mentioned any glandular swelling. Barthez and Rilliet once found them enlarged to the size of pigeon's eggs, grayish-red on section, soft, and filled with some fluid, but not suppurating. Bartels observed enlargement of the submaxillary glands in a woman of 40 and a child of three years. According to Bruns the lymph glands are not usually enlarged. Carrière-Montjosieu says the glands are not enlarged unless there is an added microbic infection. An enlargement of the submaxillary glands has been observed by later writers, as Henoch and Filatov.

Pain.—Noma is generally described as a painless affection (Allbutt, Blumer and MacFarlane, Filatov, Gierke, Tourdes). According to Holt the pain is rarely severe; in many cases it is absent. Carrière-Montjosieu reports a case of noma in which pain was intense.

Usually about the first to the third day of the gangrene there forms deep in the tissues a firm, hard, circumscribed kernel, 1–2 cm. in diameter. The overlying skin is then tense, shining as if oiled, often violet or marmolated. The hard kernel may not form until later, even on the sixth to the ninth day, and shortly before death. It was never absent in the cases observed by Barthez and Rilliet. Later it may soften because of gangrenous disintegration of the tissues entering into its formation. According to Filatov: "In the beginning of the disease there always appears a tumor in the cheek, the integument being pale, not hot, and painless on pressure."

In many cases an eschar forms on the cheek. According to Baron it occurs on the second or third day. In Destries' cases it occurred on the sixth day. Out of 21 cases observed by Barthez and Rilliet, it appeared between the third and seventh days in eight, on the 12th day in one, and on the 17th day in one. At the place where the eschar is to form the skin becomes violet and then black. Often a vesicle forms at the summit of the swelling of the cheek or lip, and soon it becomes

included in a gangrenous spot. The gangrene of the skin tends to extend quite rapidly, and is surrounded by edematous tissues. Barthez and Rilliet describe two distinct zones surrounding the circular eschar which were first pointed out by Bouley and Caillault. The first zone is from 5 to 6 mm. wide, circumscribes the gangrenous eschar, is gray, and bleeds freely. The second zone is formed of a diffuse edema which spreads more or less widely. The skin at the border of the edema is usually pale, while that near the gray zone is at times moderately or quite red.

If the eschar becomes circumscribed it separates at the edges, and finally falls away with all the underlying tissues down to the mucous membrane, so that a perforation results, through which flows saliva charged with gangrenous masses from the mouth, and exposing to view the interior of the mouth and nose. The edge of the perforation remains swollen, hard and red, or marked by gangrenous shreds.

If healing occurs the borders become clean and finally assume the appearance of a granulating surface. As the edges approach a fistula remains, which may be permanent or may completely close.

II. VULVAR AND AURAL GANGRENE.

According to Kraus, vulvar and aural gangrene have a course similar to buccal, but multiple areas are more common. Vulvar gangrene usually originates in an ulceration of the mucous membrane of the labia, but may begin deep in the tissues (Henoch). Hoit, who has observed noma of the ear seven times, found it always preceded by chronic otitis media. It began in the deeper structures of the canal, the first symptom noticed being a nodular swelling, just beneath the ear, crowding the lobe upward. Shortly afterward there appeared a dirty brown discharge with a gangrenous odor. The gangrene extended gradually, until in some cases the whole side of the face and head was involved.

COURSE, DURATION, AND TERMINATION.

Course.—According to Tourdes there are three periods in the course of noma:

1. The period of ulceration of the mucous membrane, edema of the face, and the formation of the central kernel, lasting two to three days.

2. The period of gangrene, extending from five to 12 days.

3. The period of general infection.

Duration.—Noma has a rapid course rarely extending over more than two weeks. Death usually occurs between the eighth and 14th days.

Relapses.—There are few records of relapses on account of the disease being so fatal (Barthez and Rilliet). Berthe (1754), quoted by Tourdes, saw a child attacked by noma twice. Hueter reported a case having a relapse followed by recovery. Ziegler observed two relapses in a case. According to Gierke in seven cases, beginning healing appeared and death followed from pneumonia. In one case observed by him a relapse occurred, and the child recovered a second time in six months. In another case of Gierke's the second attack, occurring two years after the first, proved fatal.

DIAGNOSIS.

Noma is easily recognized. The diagnosis is based on the gangrenous odor of the mouth, the flow of ichorous and fetid saliva, the grayish ulceration of the mucosa, the central kernel, the yellowish or brownish spot on the skin, the rapid course, and destruction of tissue.

Taupin considered (1839) noma and pseudo-membranous or ulcerative stomatitis the same in general causation, and nature. This view is held generally by modern observers who have studied the bacteriology of the affections (Buday, Rona, and others).

Malignant pustule always begins in the outside skin, which rarely if ever is the case with noma.

Gangrenous aphthae is a disease of the same nature, but there is only a localized eschar, while in noma gangrene is diffuse.

COMPLICATIONS.

As noma always develops after some other disease it is difficult to specify the complications.

The most frequent one is pneumonia. It was present in 58 out of 63 cases collected by Tourdes. It was absent in only two out of 21 cases examined by Barthez and Rilliet.

Pleurisy and enteritis have been observed to develop in the course of gangrene; but the complications most grave are gangrene in other parts of the body (Tourdes). In eight out of 36 cases reported by Taupin, gangrene was present in the lung, pharynx, esophagus, and stomach. Barthez and Rilliet found gangrene of the lungs and pharynx in four out of 20 cases. Coincident gangrene of the vulva has been observed by Richter and others.

Hemorrhage rarely occurs. Hueter saw a fatal case. There was a severe nasal hemorrhage in the case observed by us.

PROGNOSIS.

All observers agree that noma is usually fatal. According to Tourdes the 30 cases seen by Baron were all fatal, as well as the 36 cases of Taupin. Tourdes collected 239 cases from the literature, of which 176 died, making a mortality of 73 per cent.

According to Tourdes the factors which influence mortality are age, both extreme youth and old age being unfavorable; bad hygienic surroundings; complications, especially pneumonia; the nature and time of treatment. The extent of destruction of tissue is not always the cause of death.

Cases in which recovery occurs almost always are uncomplicated by any severe affection and those in which the appetite and strength are preserved throughout the entire course. If recovery does occur it requires weeks and even months for healing according to Gierke. If the part of the jaw containing rudimentary teeth has been destroyed, the mouth will remain toothless. Speech is always affected. Generally a great deformity results. In healing after gangrene of the vulva, fistulae, stenosis, or atresia of the vagina may result (Holt). Nine out of 14 cases seen by Mayr died. The five saved were those with least extension of the disease and best body resistance.

Bouchut says that gangrene of the mouth which involves a large part of the face is fatal. Gangrene of the mouth, according to him, heals only at its onset under the influence of deep cauterization, which is repeated two or three times daily with hydrochloric acid.

Gierke observed 18 deaths and two recoveries. No cases of his died after the second week. Some cases of circumscribed noma without deeply extending involve-

ment ended fatally. All of the cases of noma of the genitalia and auditory region observed by him were fatal.

Springer (1904) gives a table of all cases of noma in the Children's Hospital in Prague, between 1888 and 1903, during which time they were treated by means of excision. Twenty-three cases were observed, two recovered, giving a mortality of 90.5 per cent. Of the 16 cases operated upon 14 died, giving a mortality of 87.5 per cent. Of the seven cases not operated upon, seven died giving a mortality of 100 per cent.

TABLE 1.

SUMMARY-PROGNOSIS.

Author	Year	No. of Cases	Died	Recovered	Percentage
Wood	1816	12	10	2	83
Tourdes	1848	239	176	63	73
Mayr	1852	14	9	5	64
Barthez and Rilliet, Baron and Destries	1855	29	26	3	89
Bruns	1859	413	290	123	70
West	1866	10	8	2	80
Gierke	1868	18	16	2	88
Steiner*	1876	108	103	5	95
Day	1881	7	6	1	85
Woronichin	1887	22	19	3	86
Blumer and MacFarlane	1901	16	14	2	87
Springer	1904	88	83	5	94
Total		976	760	216	77.8

*Cited by Bohn.

TREATMENT.

The high mortality under the treatment employed by all observers serves to emphasize the fact that most of the measures which have been used are of little or no value. Stoppage of cases in the early stages has been reported as due to various local measures. It is in the early stage that something may be expected. The prompt removal of the tissues involved, together with some apparently healthy tissue, offers a reasonable hope of stopping the progress of the disease. Such measures have yielded good results in the hands of Ranke, Springer, and others. The knife is used first to remove the necrotic tissues and is followed by the free use of the actual cautery. Of course this is done under the anesthesia, and the likelihood of favorable results is in proportion to the thoroughness with which the operation is carried out.

Aside from free removal, local antiseptic measures are advisable, but can scarcely be looked upon as curative.

Patients recovered from noma should not be subjected to plastic operations for the repair of deformities for a number of months after complete recovery, because of the danger of the recurrence of gangrene in the operation wounds.

Aside from measures directed directly toward the local condition, every effort is to be made to support the strength of the child by suitable food and tonic measures.

Of more importance than to cure is to prevent the occurrence of noma. This must be accomplished by placing children who are liable to the disease in the best hygienic conditions where they will be freely supplied with good food, fresh air, and sunshine. The mouths and genitalia of delicate children who have been reduced by infectious diseases should be carefully watched. Any ulcerative lesion of the mucous membrane is to be vigorously cared for until healed. If any gangrene appears,

radical measures should be carried out at once. Cases of noma should be isolated, since the danger of contagion is always present.

AUTHORS' CASE.

The following case was observed in the Hospital of the Memorial Institute for Infectious Diseases in the service of Dr. Frank Billings and Dr. Alexander F. Stevenson, to whom we wish to express our thanks for the opportunity of reporting the case.

Clinical record.—O. A., female; eight years. The patient's family history is negative. She has had none of the diseases of childhood. A few weeks previous to her entrance she suffered from an alveolar abscess which caused considerable swelling of the left side of her face. On September 21, 1904, the patient was taken ill with sore throat, vomiting, diarrhea, and fever. The following day a light red rash appeared and a diagnosis of scarlet fever was made. She was admitted on September 24.

She is a poorly nourished child. There is a slight conjunctivitis of both eyes. She has considerable muco-purulent discharge from the nose. Her lips are bleeding and covered with crusts. Her teeth are badly decayed and covered with tartar. Both tonsils are much swollen, of a brilliant red color, and are free from exudate and membrane. The mucosa of the whole mouth is of a bright scarlet color. Her tongue is free from coating, very red, and the papillae stand out prominently. There is a large amount of grayish mucus in the throat.

Her whole body with the exception of the area around the mouth is covered with a brilliant red rash, disappearing readily on pressure. It is punctate in character, except on the hands and feet, where it is uniform. Both drum membranes are pinker than normal.

The posterior cervical, axillary, and inguinal glands are the size of peas. The anterior cervical glands are the size of beans individually, and altogether form a mass the size of a walnut.

Heart and lungs are normal. Temperature at entrance, 102° F.; pulse, 140; respiration, 28. Stools are green and contain mucus.

Smears from the tonsils show leucocytes filled with streptococci and a few diplococci. Both organisms are also found outside of the cells. Cultures on blood serum from the tonsils show streptococci and staphylococci and a few bacilli. Blood cultures are sterile. Cultures from the nose show staphylococci.

September 26.—A thin white, exudate has formed on both tonsils. It is easily removed without leaving a bleeding surface. Smears and cultures show streptococci and diplococci. Catheterized specimen of urine shows a trace of albumin and a few granular casts. She is delirious at night.

September 27.—A membrane has formed over both tonsils and the anterior pillars of the fauces. It is thick, soft, and of a buff color. Smears show the same organisms as before.

September 28.—The left cervical glands are enlarged, being the size of two walnuts.

September 29.—Desquamation has commensed. Smears from the membrane on the tonsils show streptococci, spirilla, and diplococci.

October 2.—There is a moderate amount of yellowish purulent discharge from the left ear.

October 3.—There is a purulent discharge from the right ear. Cultures from the ears show streptococci and staphylococci. The tonsils appear less swollen and

red. The membrane is present only on the anterior pillars. There is no discharge from the nose. There is paralysis of the pharynx, fluids drunk running out of the left nostril.

October 4.—The left side of the face is swollen and tender. The cervical glands on the left side extend from the mastoid process to the angle of the jaw. Cultures from the throat show streptococci and staphylococci. Pulse is weak. The tonsils appear almost normal in color, slightly swollen and free from membrane. There is more discharge from the left ear than from the right. The left side of the face is more swollen and slightly pink in color.

October 6.—There is an increase in the muco-purulent discharge from the left nostril. Smear preparations show many spirilla, fusiform bacilli and streptococci, diplococci and pseudodiphtheria bacilli. There is considerable swelling and tenderness of the superior maxilla of the left side. The upper and lower eyelids of the left eye are swollen, and there is some purulent discharge from it. Cultures from the discharge show staphylococci, pseudodiphtheria bacilli and streptococci. Blood cultures are sterile. Catheterized specimen of urine shows albumin, amorphous urates, epithelial cells, a few hyaline and granular casts, and leucocytes. Cultures from the urine show streptococci.

October 7.—Cultures from the nose give pseudodiphtheria bacilli, streptococci, and staphylococci. The swelling of the cheek and lip is greater and more tense. There is a large amount of muco-purulent discharge tinged with blood from the left side of the mouth, smears from which show spirilla, fusiform bacilli, streptococci, and pseudodiphtheria bacilli. The left side of the superior maxilla and the teeth on that side are covered with a yellowish green membrane. Her breath is very fetid. The upper four teeth beginning with the incisor on that side are loose.

October 8.—The eyelids of the right eye are swollen. The gums separate from the teeth on the left side, especially in front of the first tricuspid tooth, where a probe can be inserted for a distance of an inch, at which point the bone seems to be denuded. The membrane over the superior maxilla is partially separated and hangs into the mouth. At 4 P. M. the skin over the left molar bone is observed to be slightly blue in color.

October 9.—In the morning the discoloration on the upper inner side of the left cheek extends over an area 7 cm. in diameter. The color is blackish blue. It has a well-defined, bluish line of demarkation externally, reddish internally. The area is devoid of the outer layer of the skin. The eyelids of both eyes are edematous as well as the left side of the face extending behind the ear. The right side of the forehead is also edematous. The sloughing in the mouth extends almost to the median line. The first tricuspid teeth (upper and lower) have fallen out. The left side of the upper lip externally is black and there is a blue line of demarkation. The glands on the left side of the neck are less swollen. There seems to be some fluctuation in them. Fine and coarse rales may be heard over both sides of the chest. She coughs occasionally.

October 10.—The area of necrosis on the left side of the face is almost circular, being three and a half inches in diameter. It has extended over the lower eyelid almost to the middle of her nose and upper lip. It has extended into the left nostril and into the mouth, on the upper and to a slight extent on the lower lip. The sloughing has extended beyond the median line inside of the mouth, the first incisors on the

right side being loose. At 3 P. M. there is some hemorrhage from the right nostril. The patient died at 6 P. M.

From the throat fusiform bacilli and filaments were grown in mixed cultures in sugar-free broth and ascitic-fluid broth aerobically. Anaerobically, fusiform bacilli and filaments associated with other organisms grew in ascitic-fluid broth and sugar free broth.

The fusiform bacilli and filaments did not retain Gram's stain, except in the dark spots.

Neither fusiform bacilli nor filaments grew in the cultures from the necrotic tissue of the face, which may have been due to the small amount of material used for inoculation. In addition to streptococci, staphylococci and pseudodiphtheria bacilli were isolated from the necrotic tissue.

AUTOPSY (Dr. Ruediger).

Anatomical diagnosis.—Necrosis of left side of face involving the upper jaw. Acute nephritis. Hydropericardium. Double hydrothorax. Splenic infarcts. Acute splenic tumor. Suppuration of left submaxillary glands. Swelling of tonsils and of pharyngeal walls. Broncho-pneumonia. Desquamation of scarlet fever.

The body is that of a poorly nourished girl, 3 ft., 10 in. tall. Rigor mortis is present. There is marked postmortem discoloration on the back. On the feet, legs, hands, and wrists are signs of desquamation. On the left side of the face is a very dark-bluish, nearly circular area of necrosis extending from the median line of the nose to within 2 cm. from the ear, and from the upper margin of the lower eyelid to the lower jaw. The upper eyelid also has a bluish tinge. A zone about 1.5 cm. in width around the periphery of this nearly circular area is lighter colored and has a slightly greenish tinge. This area is soft and markedly edematous; the left eyelids are especially edematous. In the central and darkest portion of this area the epidermis is broken and a small amount of slightly hemorrhagic serum exudes. This area of necrosis involes also about three-fifths of the upper jaw and roof of the mouth on the left side, and the left three-fifths of the soft palate and uvula; also a small portion of the lower gums posteriorly. The upper teeth from the left molars to the right canine are missing.

The peritoneum is everywhere smooth and glistening. There are no adhesions. There is a small amount of slightly turbid, pale yellow fluid in the peritoneal cavity. The intestines are distended with gas. The omentum contains very little fat and reaches downward to a point about midway between the ensiform and the symphysis. The liver extends a little below the costal arch. The pleurae are smooth and glistening. There are no adhesions about either lung. The right pleura contains about 200 c.c. of hemorrhagic fluid, and the left pleura contains a somewhat smaller quantity of clear straw-colored fluid.

The pericardial sac is filled with a clear, straw-colored fluid. It also contains a gelatinous clot of fibrin about as large as a small walnut. The clot is not adherent. The pericardium and epicardium appear normal.

The thyroid shows no changes.

In the upper half of the larynx there is some slaty pigmentation. Otherwise there are no changes. The trachea is normal.

The peribronchial lymph glands are soft and bloody, and swollen.

The right lung has a grayish-pink, somewhat mottled appearance. There are

several slightly depressed areas which crepitate very feebly. These are dark red in color, and vary in size from 3 to 5 cm. The cut surface of the lung is hemorrhagic and has dark-red areas, corresponding to those seen on the surface, which are more bloody and solid than the surrounding tissue. Frothy blood can be expressed from the lung. The left lung is very much like the right, and the same description applies to it.

The heart is almost as large as the owner's fist. It is firm and apparently normal. The apex is formed by the left ventricle. The endocardium, myocardium, and all the valves are normal.

The aorta is normal.

The spleen is large, soft, and light red in color. On the surface are six firm, light-grayish-pink, irregular areas which are slightly depressed. The largest measures 3×1.8 cm., and is 1 cm. in depth on the surface where these areas are seen distinctly as grayish, firm, irregular areas. The splenic pulp is very soft.

The tongue shows no changes.

The tonsils and pharyngeal walls are swollen and bluish, but there is no ulceration.

The esophagus is normal. The liver shows no changes. The gall bladder contains about one ounce of straw-colored bile. The pancreas is normal. The adrenals are large and soft.

The kidneys are very much alike. They are large, soft, and pale yellowish-gray. They seem to be bloodless. The cortical markings are indistinct and the portions between the pyramids stand out more prominently than other parts. There are some areas that are whiter than others. The cortex measures 1–1.5 cm. in thickness. The capsule strips readily, leaving a fairly smooth surface.

The ureters and bladder are normal.

The retroperitoneal lymph glands in the region of the kidney are large and pink.

The submaxillary glands on both sides are as large as small hickory nuts and are quite firm. On the left side are some very soft lymph nodes containing pus.

Bacteriologic examination.—The streptococcus in pure culture was isolated from the pericardial fluid, the right and left pleural cavities, the spleen and the necrotic area of the face. The streptococcus and the colon bacillus were isolated from both lungs, the right kidney, the liver, and the peritoneal fluid.

Smears from the patient's internal organs showed neither spirilla nor fusiform bacilli; those from the tonsils showed fusiform bacilli, diplococci, spirilla. Smears from the cheek tissues at line of demarkation showed fusiform bacilli, spirilla, diplococci, streptococci, and smears from the suppurating submaxillary lymph gland contain streptococci.

Histological examination.—A section of the lung shows broncho-pneumonia with edema and hemorrhage. Other sections show the same changes but to a less degree.

There is marked hyperemia of the spleen.

The periportal connective tissue in the liver is very rich in cells.

The mesenteric lymph gland shows lymphoid hyperplasia.

The kidney shows collections of mononuclear round cells.

Part of the tissue removed from the cheek is completely necrotic, no nuclei being present (absolute alcohol, paraffin, hematoxylin, and eosin). Just beyond the advancing necrosis and in the living tissue there is some accumulation of leucocytes, but it is not marked. No sharply marked demarkation zone is present. The vessels are filled with red and white blood cells. In the areolar tissue of the necrotic and

infiltrated parts, faintly staining filaments, spirilla and pointed bacilli are seen. Some of the bacilli are much curved. The bacilli stain more deeply than the other organisms.

The bacilli, filaments, and spirilla do not retain Gram's stain, if the decolorization is thorough. The bacilli hold it longer than the filaments and spirilla.

Gram-Weigert sections show that under the external layer of the skin fusiform bacilli are present in considerable numbers in the normal tissue. The blood vessels in the normal and necrotic tissue are filled with red and white blood cells. Fusiform bacilli are present in large numbers in the walls and around the vessels. A moderate number of bacilli and filaments can be seen inside the vessels. The number of bacilli is small until the subcutaneous tissue is reached, but increases as the border between the healthy and necrotic tissue is approached. The bacilli stained by this method show very irregular staining. Some are considerably curved. They are often arranged in pairs and occasionally appear like filaments. No spirilla are seen when this stain is employed.

Carbol-gentian-violet was found to be the most satisfactory stain for the organisms. A 10 per cent solution of saturated alcoholic gentian-violet in 5 per cent carbolic acid was employed for five minutes, the section having been imbedded in paraffin and treated with xylol, followed by absolute and 95 per cent alcohol. After staining for five minutes, the specimen is cleared by means of aniline oil, washed with three changes of xylol, and mounted in balsam. When this method is used the spirilla stain clearly. The specimens were found much more satisfactory than when carbol-fuchsin was employed for 24 hours. The bacilli and filaments often stain more intensely than the spirilla, but in deeply stained preparations the three appear of the same thickness, with only an occasional thicker bacillus. In the area of complete necrosis fusiform bacilli, filaments, and spirilla are all present, the spirilla generally predominating in number. Where the infiltration begins one finds more spirilla and fusiform bacilli, the spirilla being more numerous than the filaments. In the living tissue both spirilla and bacilli are present, but the spirilla are in larger numbers. Spirilla are seen in some of the thrombosed vessels. In the areolar tissue where the organisms show most clearly, one finds a network of spirilla, in which can be seen a few fusiform bacilli and filaments. A large amount of fibrin is seen throughout the sections.

Summary of Findings.

I. There is some leucocytic invasion, but no well-marked demarkation zone.

II. The fusiform bacilli and spirilla are similar to those seen in the smear preparations made from the nose and mouth before death and the necrotic tissue of the face immediately after death.

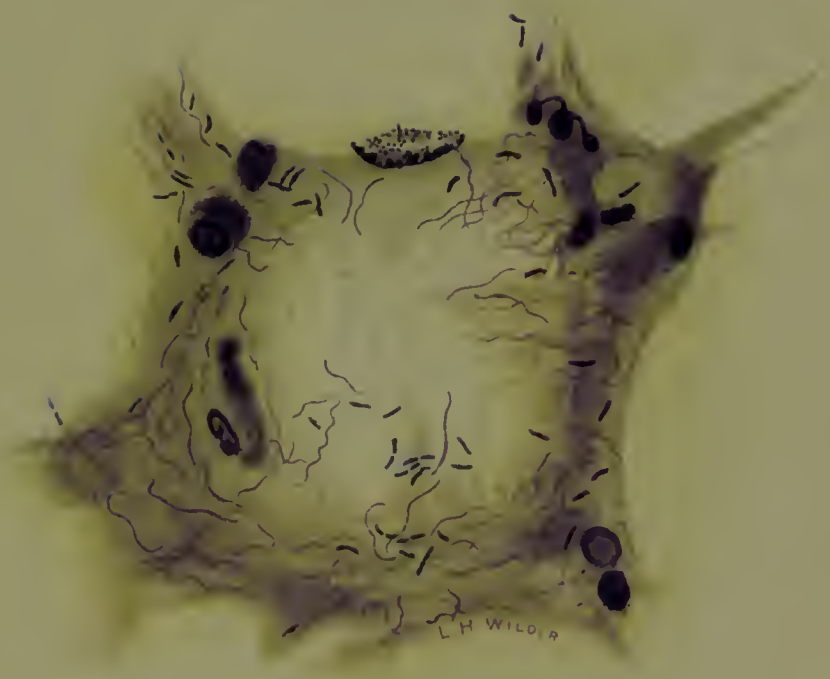
III. Both forms are present in both the necrotic and living tissue, the spirilla forms apparently being in excess in both places.

IV. The thrombosed vessels contain fusiform bacilli, filaments, and spirilla.

BIBLIOGRAPHY.

ALLBUTT. *System of Medicine*, 1897, 4, p. 339.
ALLCHIN. *Cycl. Dis. Chil.* (Keating), Phil., 1889, p. 974.

PLATE 1*a*.



Section through the living subcutaneous tissue just beyond the advancing necrosis. About ×800.

BABES AND ZAMBILOVICI. *Ann. d. Inst. de Path. et Bact. de Bucarest*, 1892, 5, p. 227. (Abs., LeCount.)
BANG. *Centralbl. f. Bakt.*, Ref., 1893, 13, p. 201.
BARTELS. *Abs. Baumgarten's Jahres.*, 1892, 8, p. 301.
———. *Dissertation*, 1892. Göttingen.
BARTHEZ AND RILLIET. German Translation, Leipzig, 1855, 2, p. 410.
BAUMGARTEN. *Baumgarten's Jahres.*, 1896, p. 496.
BISHOP AND RYAN. *Trans. Chi. Path. Soc.*, 1894, 1, 252.
———. *Jour. Am. Med. Assoc.*, 1895, 25, 1043.
BLUMER AND MACFARLANE. *Am. Jour. Med. Sc.*, 1901, 122, p. 527.
BOHN. *Handb. der Kinderkrank.*, Gerhardt, 1880, 4, p. 58.
BOUCHUT. *Handb. der Kinderkrank.*, Würzburg, 1862, p. 685.
BRAUN. *Münch. med. Wchnschr.*, 1901, 48, p. 1988.
BRÜNING. *Jahrb. f. Kinderheilkunde*, 1904, 60, p. 631.
BRUNS. *Handb. der prakt. Chir.*, 1859, 2, p. 60.
BRYDON. *Brit. Med. Jour.*, 1882, 2, p. 838.
BUDAY. *Beiträge z. path. Anat. u. z. allgem. Path.*, Ziegler, 1905, 38, p. 255.
CARRIÈRE-MONTJOSIEU. *Thèse*, Paris, 1904.
COATES. *N. Am. Med. and Surg. Jour.*, 1826, 2, p. 1.
COMBA. *Lo Sperimentale*, 1899, p. 81.
———. *Abs. Baumgarten's Jahres.*, 1899, 15, p. 539.
DAY. *Dis. of Chil.*, Phil., 1881, p. 153.
DURANTE. *Centralbl. f. Bakt.*, Ref., 1903 , 33, p. 398.
ELDER. *Edin. Med. Jour.*, 1893, 39, p. 228.
FILATOV. *Semeiology and Diag. of Dis. of Chil.*, 1904, p. 105.
FOOTE. *Am. Jour. Med. Sci.*, 1893, 106, p. 198.
FREYMUTH AND PETRUSCHKY. *Deutsche med. Wchnschr.*, 1898, 24, pp. 232 and 600.
FRORIEP. *Chir. Kupfertafeln*, 1844, p. 458.
GIERKE. *Jahrb. f. Kinderheilk.*, N. F., 1868, 1, p. 267.
GRAWITZ. *Deutsche med. Wchnschr.*, 1890, 16, p. 318.
GUIZZETTI. *Policlinico*, Marzo, 1897.
———. *Abs. Baumgarten's Jahres.*, 1897, 13, p. 652.
GUIZZETTI. *Policlinico*, 1896, 18, p. 405.
———. *Abs. Baumgarten's Jahres.*, 1896, p. 495.
HENOCH. *Vorlesungen über Kinderkrankheiten*, 1890, p. 464.
HERFF. *Deutsche med. Wchnschr.*, 1890, 16, p. 949.
HERMAN. *Trans. Obstet. Soc. Lon.*, 1883, 25, p. 141.
HERRMAN. *Archiv of Pediatrics*, 1905, 22, p. 817.
HOFMANN AND KÜSTER. *Münch. med. Wchnschr.*, 1904, 51, p. 1906.
HOFMANN. *Beiträge zur klin. Chir.* (Bruns), 1904, 44, p. 205.
HOLT. *Dis. of Infancy and Childhood*, 1905, pp. 290 and 692.
JENSEN. *Handb. d. path. Mikroorg.*, Kolle u. Wassermann, 1903, 2, p. 693.
KÖSTER. *Centralbl. f. Chir.*, 1892, 19, p. 940.
KRAHN. *Mitt. a. d. Grenzgebieten der Med. u. Chir.*, 1900, 6, p. 618.
KRAUS. *Nothnagel's spec. Path. u. Ther.*, 1902, 16. p. 202.
LECOUNT. *Trans. Chi. Path. Soc.*, 1898, 3, p. 180.
LINGARD. *Lancet*, 1888, 2, p. 159.
LONGO. *Policlinico*, 1901, 8.

LONGO. *Abs. Centralbl. f. Bakt.*, Ref., 1903, 33, p. 398.
MASTERMAN. *St. Bartholomew's Hosp. Reports*, 1891, 27, p. 205.
MATZENAUER. *Archiv f. Derm. u. Syph.*, 1901, 55, pp. 67, 229, 394.
———. *Ibid.*, 1902, 60, p. 373.
MAYR. *Ztschr. kais. kön. Gesellsch. der Aerzte zu Wien*, 1852, p. 201.
MEIGS. *Pract. Treat. on Dis. of Chil.*, Phil, 1848, p. 163.
NICOLAYSEN. *Norsk Magazin for Lægevidenskaben*, 1896, p. 137.
———. *Abs. Brit. Med. Jour.*, Epitome, 1896, p. 8.
ORTH. *Lehrbuch d. spec. Path. Anat.*, 1887, 1, p. 613.
OSLER. *Practice of Medicine*, 1905, p. 437.
PASSINI AND LEINER. *Wien. klin. Wchnschr.*, 1899, 12, p. 743.
PERTHES. *Archiv. f. klin. Chir.*, 1899, 59, p. 111.
———. *Münch. med. Wchnschr.*, 1902, 49, p. 1969.
POLLARD. *Wien. klin. Wchnschr.*, 1905, 18, p. 1236.
RANKE. *Abs. Baumgarten's Jahres.*, 1887, 3, p. 86.
———. *Münch. med. Wchnschr.*, 1900, 47, p. 1485.
———. *Ibid.*, 1902, 49, p. 1789.
———. *Ibid.*, 1903, 1, p. 13.
———.*Abs. Centralbl. f. Bakt*, 1903, 33, p. 339.
RICHTER, A. L. *Monographie*, Berlin, 1828.
RÓNA. *Archiv f. Derm. u. Syph.*, 1903, 67, p. 259.
———. *Ibid.*, 1905, 74, p. 171.
ROSENBACH. *Handb. d. Therapie innerer Krankheiten*, 1898, 4.
ROSENBERGER. *Am. Med.*, 1904, 8, p. 161.
ROUX. *Centralb. f. Bakt.*, 1905, 39, p. 531.
RUEDIGER. *Trans. Chi. Path. Soc.*, 1903, 6, p. 45.
SAFT. *Inaug. Dissertation*, Halle, 1898.
———. *Abs. Blumer and MacFarlane.*
SAILER. *Am. Jour. Med. Sci.*, 1902, 123, p. 59.
SCHIMMELBUSCH. *Deutsche med. Wchnschr.*, 1889, 15, p. 516.
SCHMIDT. *Jahr. f. Kinderheilk.*, 1898, 48, p. 72.
SCHMORL. *Centralbl. f. Bakt.*, Ref., 1892, 11, p. 666.
SEIFFERT. *Münch. med. Wchnschr.*, 1901, 49, p. 1988.
SPRINGER. *Jahrb. f. Kinderheilk.*, 1904, 60, p. 613.
STRADA. *Bull. della Soc. Medico-Chir. di Pavia*, 1903, 2.
———. *Abs. Centralbl. f. Bakt.*, 35, Ref., 1904, p. 282.
STRUEH. *Inaugural Dissertation*, 1872, Göttingen.
TOURDES. *Thèse de Strassburg*, 1848.
TRAMBUSTI. *Abs. Centralbl. f. Bakt.*, Ref., 1902, 32, p. 612.
TUNNICLIFF. *Jour. Infect. Dis.*, 1906, 3, p. 148.
VERHOEFF. *Jour. Bost. Soc. Med. Sci.*, 1900, 5, p. 465.
WALSH. *Proc. Path. Soc. Phil.*, N. S., 1901. 4, p, 179.
WEAVER AND TUNNICLIFF. *Jour. Infect. Dis.*, 1905, 2, p. 446.
WEST. *Lect. on Dis. of Chil.*, Phil., 1866, p. 462.
WOOD. *Medico-Chir. Trans.*, 1816, 7, p. 84.
WORONICHIN. *Jahrb. f. Kinderheilk.*, 1887, 26, p. 161.
ZIEGLER. *Münch. med. Wchnschr.*, 1892, 39, p. 107.